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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,930	07/21/2003	Vicki Bowman Vance	9536-3	6465
20792 7590 09/04/2008 MYERS BIGEL, SIBLEY & SAJOVEC PO BOX 37428 RALEIGH, NC 27627				
EXAMINER				
KUMAR, VINOD				
ART UNIT		PAPER NUMBER		
1638				
MAIL DATE		DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/623,930

Applicant(s)

VANCE ET AL.

Examiner

Vinod Kumar

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 20, 23 and 26 is/are pending in the application.
- 4a) Of the above claim(s) 1-5 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20, 23 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
- Paper No(s)/Mail Date 4/1/08; 4/1/08
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Status of Objections and Rejections

1. Amendment filed in the paper of February 14, 2008 is entered.
2. Claims 1-5, 20, 23 and 26 are pending. Claims 6-19, 21-22 and 24-25 are canceled. Claims 1-5 are withdrawn.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. Rejections of claims 20, 23 and 26 under 35 U.S.C. 112, 2nd paragraph are withdrawn in light of claim amendments filed in the paper of February 14, 2008.
5. Rejections of claims 20, 23, and 26 under 35 U.S.C. 112, 1st paragraph are withdrawn in light of claim amendments and persuasive arguments filed in the paper of February 14, 2008.

Election/Restriction

5. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 31, 2006. The restriction was made FINAL in the Office action mailed on May 16, 2006.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

6. Claims 20, 23, and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection has been necessitated due to the claim amendment filed in the paper filed February 14, 2008.

Claims 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for their recitation "a strand opposite the exogenous miRNA sequence" in line 6, which is confusing since it is unclear whether the recitation is referring to the nucleotides opposite the exogenous miRNA sequence or to some other interpretation. For example, the recitation could also be interpreted such that the entire strand opposite to the exogenous miRNA sequence is also replaced. As a result, it is not clear what the metes and bounds of the claim are. It is suggested to replace "a strand" with --nucleotides--.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a

question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 20 and 23 recite the broad recitation "the secondary structure of the plant miRNA precursor" in line 12", and the claims also recite "including double strandedness and mismatches" in line 13 which is the narrower statement of the range/limitation.

Dependent claim 26 is also rejected because it fails to overcome the deficiencies of claim 20.

Appropriate correction/clarification is required.

Claim Rejections - 35 USC § 103

7. Claims 20, 23 and 26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cullen et al. (US Patent Publication No. 2004/0053411, Published March 18, 2004, Filed May 5, 2003, Provisional application filed May 3, 2002) in view of Llave et al. (The Plant Cell, 14:1605-1619, Published July 1, 2002, Applicant's IDS) and Reinhart et al. (Genes and Development, 16:1616-1626, Published July 1, 2002) for the reasons of record stated in the Office action mailed November 14, 2007. Applicant traverses the rejection in the paper filed February 14, 2008.

Applicant argues that Cullen et al. provisional fails to disclose any plant miRNAs or miRNA precursors and thus one of ordinary skill in the art would reasonably interpret

that constructs described in Cullen et al. provisional based on animal miRNA precursors are intended to function in a plant cell (response, paragraph bridging pages 7 and 8).

Applicant's arguments have been carefully considered but are deemed to be unpersuasive.

It is noted that Cullen et al. provisional also teach existence of naturally occurring plant miRNA molecules that can be used to design an artificial miRNA molecule having an exogenous miRNA sequence which is complementary to a plant mRNA target to inhibit its expression. It is also noted that Cullen et al. provisional also suggest making virus resistant plants using modified miRNA molecules specifically designed to inhibit expression of plant viral genes. See in particular, pages 2-3; page 9, lines 2-3 of Cullen et al. provisional.

Applicant further argues that Cullen et al. do not teach a plant stably transformed with an miRNA precursor construct as instantly claimed (response, page 8, lines 16-27). Applicant further argues that Cullen et al. do not describe an exogenous miRNA sequence that replaces an endogenous miRNA sequence, wherein the exogenous miRNA sequence maintains the length of the endogenous miRNA sequence. Applicant further argues that Cullen et al. fail to teach or suggest that the modified miRNA precursor maintains the secondary structure including double strandedness and any mismatches (response, paragraph bridging pages 8 and 9). Applicant further argues that Figures 3A and 5 of Cullen et al. do not teach or suggest the importance of secondary structure and bulges in the modified miRNA precursor. Applicant further argues that Cullen et al. teach away from a miRNA precursor wherein the endogenous

miRNA sequence within the stem is replaced with an exogenous miRNA sequence while maintaining the length of the endogenous miRNA and the secondary structure of the native miRNA precursor as instantly claimed. Applicant also argues that Cullen et al. teachings also suggest that variations in loop structure can also be tolerated and thus one skilled in the art would not have concluded that maintaining the secondary structure of the modified miRNA precursor was important for inhibiting a target gene expression (response, 2nd paragraph of page 9 through the end of 2nd paragraph of page 11). Applicant further argues that Llave et al. and Rheinhart et al. fail to remedy the deficiencies of Cullen et al. Applicant further argues that the cited references or in general the knowledge of those of ordinary skill in the art would not have arrived at the claimed invention (response, page 12, lines 1-25).

Applicant's arguments have been carefully considered but are deemed to be unpersuasive.

It is maintained that Cullen et al. teach designing an artificial miRNA precursor by modifying a naturally occurring miRNA precursor sequence with an exogenous miRNA to target and post-transcriptionally silence a gene of interest in a cell. The reference teaches that said modification comprises incorporating an miRNA sequence of interest into said miRNA precursor by substituting stem sequences of its native miRNA to generate miRNAs suitable for use in inhibiting expression of any target gene of interest in any host cell including a plant cell. The reference clearly teaches that bulges may be present in the sequence. The reference further teaches expressing said artificially designed miRNA precursor from a DNA expression vector in any host cell, including a

plant cell. The reference also teaches that the modified or artificial miRNA precursor undergoes normal biogenesis to release non-native miRNA which participates in post-transcriptional gene silencing of the target gene of interest. See US Patent Publication No. 2004/0053411 at paragraphs 0009; Figures 1-8; paragraphs 0022, 0024-0027, 0029, 051-0053, 0057-0058.

In response to Applicant's argument that Cullen et al. do not teach maintaining the secondary structure of the modified plant miRNA precursor, it is maintained that it would have been obvious and within the scope of an ordinary skill in the art to maintain the secondary structure of the modified plant miRNA precursor because it was unknown what the effect of removing the secondary structure would be, it would have been obvious not to alter it. Since known naturally occurring plant miRNA precursors have mismatches (bulges) in the miRNA* (the nucleotide sequence opposite the miRNA), it would have been obvious and within the scope of one of ordinary skill in the art to maintain said bulges in the modified miRNA precursor to preserve the secondary structure and free energy exactly the same as that of a naturally occurring miRNA precursor. One of ordinary skill in the art would have been motivated to do so for the purpose of avoiding any possible problems during processing of the miRNA precursor. It is also noted that that the secondary structure of the modified miRNA precursor would have been maintained, if the modified miRNA precursor was derived from a naturally occurring miRNA precursor lacking bulges (mismatches) in miRNA* (strand opposite miRNA). That is, if the miRNA and miRNA* in the naturally occurring miRNA precursor

were fully complementary, there would be no need to make modifications to preserve the positions of bulges (mismatches) in the modified miRNA precursor.

It is further maintained that Llave et al. teach a number of plant miRNA precursors comprising an endogenous miRNA sequence. The reference also teaches that plant miRNA precursors contain short and simple stem-loop structures. The reference further teaches that plant miRNAs are small (predominately 21 to 24 nucleotides in length), arise by processing of miRNA precursor transcripts (~ 70 nucleotides) containing imperfectly paired stem structures in a Dicer-dependent manner. The reference further teaches cloning, sequencing and predicting secondary structures of said precursors which are capable of undergoing normal biogenesis to produce miRNA. The reference further teaches that plant miRNAs comprise a sequence which is complementary to a portion of an endogenous gene sequence whose expression is regulated by said miRNA sequence through perfect or nearly perfect binding to the endogenous target sequence. The reference also teaches a method of making a transgenic plant comprising transformation of a plant with a DNA construct comprising a mRNA inhibitory sequence (dsRNAi) operably linked to a promoter functional in a plant. See in particular, page 1605, abstract; page 1608, table 1; page 1609, figure 4; page 1611, table 2; page 1612, table 3; page 1613, figure 6; page 1614, figure 7; page 1617, sequence accession numbers.

It is further maintained that Reinhart et al. teach plant miRNA precursors comprising an endogenous miRNA sequence which is released during the processing of the miRNA precursor to play a role in post-transcriptional gene regulation of specific

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endogenous plant gene(s). The reference further teaches cloning, sequencing and predicting fold-back secondary structures (using RNAfold program) of said precursors which are capable of undergoing normal biogenesis to produce miRNA. Reinhart et al. also teach that said plant miRNA precursor comprises few mismatches in the miRNA sequence resulting in bulges. See in particular, abstract; page 1618, table 1; page 1619, figure 1; page 1622, figure 4.

It is, therefore, maintained that at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to use the method of silencing the expression of a desired gene in a cell as taught by Cullen et al., to silence a desired gene in a plant or plant cell. It would have been obvious to use a recombinant DNA encoding a plant miRNA precursor sequence as taught by Llave et al. or Reinhart et al. and modify the plant miRNA precursor sequence by replacing the native miRNA sequence with an exogenous miRNA sequence which is complementary to a gene transcript of interest for down-regulating or silencing the expression of said desired gene in a plant cell or plant. One would have used any plant transformation vector and method to make the plant cell or plant, including the one taught by Llave et al.

Given that Llave et al. and Reinhart et al. teach that a plant miRNA precursor comprising a native miRNA sequence which regulates the expression of a specific plant gene, and Cullen et al. teach designing artificial (same as modified) miRNA precursors comprising incorporating an exogenous (non-native) miRNA sequence of interest into a naturally occurring miRNA precursor, one of ordinary skill in the art would have been motivated to modify a naturally occurring plant miRNA precursor by incorporating an

exogenous miRNA sequence which is complementary to a target transcript of interest within the plant. One of ordinary skill in the art would have been motivated to do so for the purpose of down-regulating the expression of any target gene of interest, depending on one's desired end.

Given that many native miRNA sequences contain mismatches or "bulges" as seen in Llave et al. and Reinhart et al., it would have been obvious to maintain the size, and positions of mismatches of the native miRNA secondary structure in the non-native miRNA sequence of the modified plant miRNA precursor, to avoid any possible problems during processing of the miRNA precursor. Thus it would have been obvious and within the scope of one of ordinary skill in the art to have arrived at the claimed plant cells or plant exhibiting reduced expression of the target gene with a reasonable expectation of success.

Given that Cullen et al. teach that transcribing a miRNA precursor from a vector in a plant cell host opens up the possibility of long term stable gene-silencing of a target gene of interest, one of ordinary skill in the art would have been motivated to express said modified plant miRNA precursor sequence in a transgenic plant for the purpose of studying the function of a target gene of interest in growth and development for example, with a reasonable expectation of success. Obviously seeds would have also been produced for the purpose of propagation of said transgenic plants.

Thus, the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

Conclusions

8. Claims 20, 23, and 26 remain rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vinod Kumar whose telephone number is (571) 272-4445. The examiner can normally be reached on 8.30 a.m. to 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571) 272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ashwin Mehta/

Primary Examiner, Art Unit 1638